REMARKS

In the Office Action, claims 1-3, 5,7,9, 19-20 and 23-25 are rejected under 35 U.S.C. §112, first paragraph; claims 1-3, 5, 7, 9, 19-20 and 23-25 are rejected under 35 U.S.C. §112, second paragraph; and claims 1-3, 5, 7, 9, 19-20 and 23-25 are rejected under 35 U.S.C. §103. Claims 1-30 have been canceled without prejudice or disclaimer; and claims 31-44 have been newly added. Applicants believe that the rejections have been overcome at least for the reasons as detailed below.

In the Office Action, claims 1-3, 5, 7, 9, 19-20, and 23-25 have been rejected under 35 U.S.C. §112, first and second paragraphs. As previously provided, claims 1-3, 5, 7, 9, 19-20, and 23-25 have been canceled without prejudice or disclaimer, and thus, the rejections pursuant to 35 U.S.C. §112, first and second paragraphs should be withdrawn in view of same.

Further, Applicants believe that newly added claims 31-44 satisfy the requirements pursuant to 35 U.S.C. §112 as fully supported in the specification and detailed below. Of the newly added claims, claims 31 and 38 are the sole independent claims. Claim 31 recites a method for manufacturing a glucose polymer-based solution. The method includes providing a glucose polymer in a powder form; conducting a modified bioburden test on the powder form of the glucose polymer to determine a source of peptidoglycan, the source including *Alicyclobacillus acidocaldarius*; preparing a glucose polymer solution derived from the powder form of the glucose polymer; processing the glucose polymer solution including sterilization thereof; adding a reagent to the glucose polymer solution wherein the reagent is derived from a silkworm larvae plasma and that is reactive with peptidoglycan; and using the glucose polymer solution to make a peritoneal dialysis solution if it is determined that about 10 ng/mL or less of peptidoglycan is present in the glucose polymer solution.

Claim 38 recites a method of testing for a peptidoglycan contaminant. The method including conducting a modified bioburden test on a glucose polymer in a powder form to determine a source of peptidoglycan, the source including *Alicyclobacillus acidocaldarius*; preparing a glucose polymer solution derived from the powder form of the glucose polymer; processing the glucose polymer solution including sterilization thereof; adding a reagent to the glucose polymer solution wherein the reagent is derived from a silkworm larvae plasma and that is reactive with peptidoglycan; and determining whether peptidoglycan is present in the glucose

polymer solution at a level exceeding 10 ng/mL that is sufficient to cause peritonitis if the glucose polymer is used in a peritoneal dialysis solution.

As further supported in the specification, the claimed invention relates to methods and compositions that employ modified bioburden testing and the detection of peptidoglycan in peritoneal dialysis solutions, raw materials that can be used to make the peritoneal dialysis solutions and/or at any suitable stage in the manufacturing of same. The inventors have surprisingly discovered a novel cause of aseptic peritonitis, namely aspectic peritonitis associated with gram positive contamination (e.g., *Alicyclobacillus acidocaldarius*) of a dialysis solution. Peptidoglycan is a major component of a gram positive bacterial cell wall and thus can serve as a marker for gram positive bacteria. Thus, testing for peptidoglycan can be utilized to effectively prevent peritonitis in patients that use the peritoneal dialysis solutions, such as peritoneal dialysis solutions that contain a glucose polymer including an icodextrin and the like. See, Applicants' specification, page 6 at lines 13-23.

Icodextrin is derived from corn starch, a natural product. The inventors have surprisingly found that some natural products, such as corn starch, are likely to be contaminated with the acidophilic thermophilic bacteria *Alicyclobacillus acidocaldarius*, and have further found that this is due to the high temperature and low pH conditions used to process this starch hydrolysate. See, Applicants' specification, page 6 at lines 23-27. In general, peritoneal dialysis solutions and parenteral solutions have not been recognized to have been contaminated by this specific type of bacteria (e.g., *Alicyclobacillus acidocaldarius*) or its degradation products (e.g., peptidoglycan). This is mainly because the current testing procedure for microbial contamination of peritoneal dialysis solutions and parenteral solutions in general are not capable of detecting same. See, Applicants' specification, page 7 at lines 3-7.

To address this problem, Applicants have applied a modified bioburden test under new conditions to detect the presence of *Alicyclobacillus acidocaldarius*. For example, the new conditions require a pH of less than about 5.0 and temperatures above room temperature. See, Applicants' specification, page 7 at lines 8-16. In contrast, bacterial cultures associated with parenteral products including peritoneal dialysis solutions are typically performed at neutral pH using an incubation temperature between 20-35°C. These are suboptimal conditions for the growth of *Alicyclobacillus acidocaldarius* that require an acid medium and elevated temperature

for growth, and thus, routinely employed "sterility definitions" and the supporting assays may fail to detect microorganisms that do not grow under conventional conditions. See, Applicants' specification, page 12 at lines 1-12.

Under the modified bioburden test, if the Pharmacopoeia standards are met, the glucose polymer can then be safely used to make the peritoneal dialysis solution. See, Applicants' specification, page 7 at lines 12-17. If not, heat and sterile filtration procedures and the like can be employed to eliminate the bacteria in the near final product. Even so, Applicants have discovered that typically-employed sterilization and filtration processes may not be sufficient to eliminate peptidoglycan contamination, where the peptidoglycan may remain as a degradation product of the *Alicyclobacillus acidocaldarius* even after such processing. See, Applicants' specification, page 17 at lines 22-28. Through further investigation, Applicants determined and established that 10 ng/mL or less of peptidoglycan can be present in a peritoneal dialysis solution without causing peritonitis. See, Applicants' specification, pages 16 and 17. Therefore, Applicants have discovered a two-stage testing procedure for a glucose polymer-based material to ensure the sterile and safe use of such material in peritoneal dialysis solutions as required by the claimed invention and as fully supported by the specification as previously discussed.

Accordingly, Applicants respectfully request that the rejections pursuant to 35 U.S.C. §112, first and second paragraphs, be withdrawn.

In the Office Action, claims 1-3, 5, 7, 9, 19-20, and 23-25 have been rejected under 35 U.S.C. §103 in view of Gokal et al., Martin et al., Goffin et al., Tsuchiya et al., the May 2002 publication, Tsuchiya et al., and Ashida et al.. As previously provided, claims 1-3, 5, 7, 9, 19-20, and 23-25 have been canceled without prejudice or disclaimer, and thus, the rejection with respect to same should be rendered moot. Further, Applicants believe that the cited art, even if properly applied and combinable, should be considered distinguishable from newly added claims 31-44.

As previously discussed, the new claims 31-44 include two independent claims, namely claims 31 and 38. Claim 31 recites a method of manufacturing a glucose polymer solution; and claim 38 recites a method of testing for a peptidoglycan contaminant. The claims generally describe a two-stage testing procedure for a glucose polymer-based material to ensure the sterile and safe use of such material in peritoneal dialysis solutions as previously discussed. In the first

stage, a modified bioburden test is conducted to determine the presence of a source of peptidoglycan, namely the presence of *Alicyclobacillus acidocaldarius*. The modified biodurden test requires test conditions, such as pH and temperature, that are different from typically employed conditions, such as neutral pH and room temperature. As further defined in claims 35 and 42, the modified bioburden test is conducted at a pH less than about 5.0, and as further defined in claims 36 and 43, the modified bioburden test is conducted at a temperature above room temperature. Under the modified testing conditions as claimed, this ensures that the source of peptidoglycan (e.g., *Alicyclobacillus acidocaldarius*) can be properly identified if present in the glucose polymer, and thus, further sterilization processes and the like can be conducted to remove this specific type of bacteria from a solution derived from the glucose polymer.

Even after such processing, Applicants have recognized that peptidoglycan contamination can remain in solution as a degradation product of the *Alicyclobacillus acidocaldarius* bacteria. Thus, further testing of the glucose polymer solution is required to ensure that the level of peptidoglycan does not exceed 10 ng/mL such that the glucose polymer solution can be safely used in a peritoneal dialysis solution as previously discussed.

Applicants believe that the cited art is distinguishable from the claimed invention. For example, nowhere do the cited references recognize the specific type of bacteria, namely, *Alicyclobacillus acidocaldarius*, as a source of peptidoglycan contamination in a parenteral product (e.g., peritoneal dialysis solution), let alone further recognize that modified bioburden testing conditions are required to test for the presence thereof.

Further, the Patent Office cannot properly apply the Oita reference to remedy the deficiency of same. Like the other cited references, nowhere does Oita identify *Alicyclobacillus acidocaldarius* as a source of peptidoglycan contamination, let alone as a source of such contamination in parenteral products including peritoneal dialysis solutions derived from glucose polymers. Indeed, Oita is directed to a specific type of antimicrobial agent (e.g., thionin) that can purportedly exhibit growth-inhibitory activity against acid-resistant and heat-resistant bacteria. See, Oita, Abstract.

Moreover, nowhere does the cited art, even if properly applied and combinable, disclose or suggest a two-stage testing procedure that combines both the modified bioburden test and the peptidoglycan test as claimed. Again, the claimed two-stage testing procedure is provided to

ensure the sterile and safe use of a glucose polymer material (e.g., powder and/or solution) for use in peritoneal dialysis solutions. Even if the *Alicyclobacillus acidocaldarius* bacteria can be effectively eliminated through sterilization and the like, Applicants have discovered that peptidoglycan contamination may exist as a degradation product of the *Alicyclobacillus acidocaldarius*, and thus, the additional testing for peptidoglycan and at specified levels as recited by the claims is required to ensure the safe and effective use of peritoneal dialysis solutions made from such tested glucose polymer material.

Therefore, Applicants believe that the cited art, even if properly applied and combinable, is distinguishable from the claimed invention. Accordingly, Applicants respectfully request that the obviousness rejection be withdrawn in view of same.

Applicants note that two references, namely the Kanny G. et al. and Seow Ying-Ying T. et al. publications, have not been entered for examination purposes as the Examiner did not initial each citation thereof on the PTO Form 1449 attached to the Final Office Action dated November 14, 2005. The Examiner alleges that the copies were not received. However, Applicants received a date stamped post card indicating that the cited references were received by the Patent Office. In the spirit of cooperation and an effort to resolve this issue in an expeditious manner, Applicants are submitting concurrently with this response a supplemental IDS that again cites the references at issue, and further Applicants have provided a copy of each reference. Accordingly, Applicants respectfully request that the references be entered for examination purposes and that the Patent Office provide Applicants with acknowledgment regarding same.

For the foregoing reasons, Applicants respectfully submit that the present application is in condition for allowance and earnestly solicit reconsideration of same.

Respectfully submitted,

BY _____

Thomas C. Basso (46, 541)
Cust. No. 29200

Dated: March 8, 2006